EXHIBIT A

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Drug Safety and Effectiveness

May 21, 2019

Food and Drug Administration
Division of Freedom of Information
Office of Shared Services
Office of Public Information and Library Services
12420 Parklawn Drive
ELEM-1029
Rockville, MD 20857

Re: FREEDOM OF INFORMATION ACT REQUEST

To Whom It May Concern:

My name is Caleb Alexander. I am a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health. This letter constitutes a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552, for records related to the FDA REMS program related to zolpidem.

Background

Risk Evaluation and Mitigation Strategies (REMS) of the Food and Drug Administration (FDA) represent an important regulatory tool that the FDA uses to optimize the safe use of approved therapeutics. As with any risk evaluation and mitigation program, the success of the REMS depends critically upon the quality and comprehensiveness of data that is used to guide regulatory decision-making. While the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversight of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

This request concerns the REMS for a particular drug, zolpidem, marketed under the brand name Zolpimist by Aytu BioScience ("Aytu") and under the brand name Edluar by Meda Pharmaceuticals ("Meda"). Zolpimist (Oral Spray) and Edluar (sublingual tablets) were subject to a product-specific REMS from 2008 to 2011 that required a medication guide. The REMS was instituted because of the complex sleep-related behaviors and severe anaphylactic reactions associated with using these zolpidem products. I am interested in the Zolpidem REMS documents to study the rationale that led to the FDA's decision to release zolpidem from its REMS and to

better understand why Zolpimist and Edluar were subject to a REMS while other products in its class (e.g. Ambien) were not.

Requested Records

I seek release of the following:

Any records relating to the REMS for zolpidem(Zolpimist/Edluar) from 2007 through 2013 including:

1. All correspondence between the FDA and Aytu, Meda or any NDA for zolpidem (Zolpimist, Eluar) and any other manufacturers of this product including:
    a. FDA's initial evaluation assessing whether a REMS is needed for zolpidem
    b. FDA's written correspondence explaining that a REMS is necessary
    c. Aytu's, Meda's and any other manufactuer of this product's proposed REMS plans, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. Aytu's, Meda's and any other manufactuer of this product's REMS supporting documents, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the proposed REMS plan
    f. FDA's evaluation of the proposed supporting document
    g. Aytu's, Meda's and any other manufactuer of this product's proposed modifications, including elimination, to the approved REMS plan
    h. FDA's correspondence to Aytu and/or Meda and/or and any other manufactuer of this product approving or denying the modifications, including elimination, to the approved REMS plan
    i. Any explanations by the FDA regarding their final decision about the REMS plan
2. All REMS Assessment Reports submitted by Aytu, Meda and any other manufactuer of this product to the FDA, including:
    a. The first Assessment Report submitted due on September 13, 2010
    b. The Interim Assessment with Patient KAB due on June 11, 2011,
    c. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to Aytu, Meda and any other manufactuer of this produc between December 2008 and September 2011.
4. Any FDA REMS Modification Review reports sent to Aytu, Meda and any other manufactuer of this product between December 2008 and September 2011 including the October 2010 review
5. The FDA's evaluation assessing whether a REMS is needed for zolpidem, including any FDA memoranda, and the written information used by FDA in the assessment, including any data.

6. Any subsequent communication between the FDA and Aytu and/or Meda and/or and any other manufactuer of this product relating to all of the above

I request that all of these documents be produced in their native electronic formats with any attached metadata included, so long as such electronic files can be opened using standard commercially available software. If the files cannot be produced in this manner, I request that records be produced in an alternative electronic format that is text-searchable. With respect to databases, spreadsheets or similar organized sets of data, I request that the records be produced in .xls or .csv format. *See* 5 U.S.C. § 552(a)(3)(B).

Application for Expedited Processing

I request expedited processing for this request pursuant to 5 U.S.C. § 552(a)(6)(E) and 21 C.F.R. § 20.44(a)(2).

Expedited processing is appropriate here because a compelling need exists for the disclosure of the requested information. Shedding light on FDA's internal processes for instituting (and releasing) REMS is likely to have significant public health benefits, thereby reducing threats to the life or physical safety of all individuals using FDA-approved drugs. The public interest is heightened because REMS are implemented for unusually dangerous drugs where there is a concern "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1. Clinicians, researchers, and the public at large will benefit from prompt access to the requested information, to ensure that the zolpidem REMS and other REMS function well and that patients are not being harmed by REMS that are over- or underprotective.

Pursuant to 5 U.S.C. § 552(a)(6)(E)(vi) and 21 C.F.R. § 20.44(a)(2), I certify that the information in this request concerning the reasons for expedited processing is true and correct to the best of my knowledge and belief.

Application for Waiver of Fees

Pursuant to 5 U.S.C. § 552(a)(4)(A)(iii) and 21 C.F.R. § 20.46, I request waiver of fees incurred in connection with searching and copying in responding this request. I am requesting the waiver on the grounds that disclosure of the requested information is in the public interest because it is likely to contribute significantly to public understanding of the operations and activities of the government and is not primarily in the commercial interest of the requester.

Disclosure is in the public interest:

Disclosure is in the public interest pursuant to 21 CFR § 20.46(b)(1) and (2) because this request will shed light into operations or activities of the FDA that are not already public knowledge. As noted above in the Background section, while the FDA has taken important steps during the past

decade to increase transparency regarding some elements of REMS programs, remarkably little is known about how REMS programs are developed, implemented, and monitored, including regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversite of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

The circumstances surrounding the FDA's decision to create a REMS for zolpidem are not public knowledge. As noted above in the Background section, I am interested in the Zolpidem REMS documents to study the rationale that led to the FDA's decision to release zolpidem from its REMS and to better understand why Zolpimist and Edluar were subject to a REMS while other products in its class (e.g. Ambien) were not.

Disclosure is also in the public interest pursuant to 21 CFR § 20.46(b)(3) and (4) because I plan to disseminate the information I obtain from this request to the public through publication in widely distributed, high-impact, peer-reviewed medical and public health journals, as well as other media. I have an established track record of such publications, including publications based on FOIA requests to FDA. Exemplary high-impact publications based on my investigations include

- Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products. *JAMA.* 2019;321(7):676–685. doi:10.1001/jama.2019.0235
- Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med.* 2018;178(11):1451–1457. doi:10.1001/jamainternmed.2018.3931
- Qato DM, Alexander GC. Post-Marketing Drug Safety and the Food and Drug Administration's Risk Evaluation and Mitigation Strategies. *JAMA*. 2011;306:1595-1596.

The requester has no commercial interest in the information sought:

I have no commercial interest in the information sought. 45 C.F.R. § 5.54(b)(3). I am not in the business of developing or selling new drugs or biologics, and I do not stand to make a profit from the disclosure of the requested information. I have no commercial interest in these records, but rather I aim to facilitate and conduct rigorous, objective, and fair evaluation of the information sought in furtherance of public knowledge and public health.

For these reasons, a public interest waiver of fees is appropriate here. I therefore respectfully request that all fees related to the search, review, and duplication of the requested records be waived. If the search and review fees will not be waived, I ask that you contact me at the email address listed below should the estimated fees resulting from this request exceed $100.

Conclusion

Pursuant to applicable statutes and regulations, I anticipate a determination regarding expedited processing within 10 days. *See* 5 U.S.C. § 552(a)(6)(E)(ii); 21 C.F.R. § 20.44(a)(2).

If my request is denied in whole or in part, please justify all withholdings and redactions by reference to specific FOIA exemptions. I expect the release of all segregable portions of otherwise exempt material, see 5 U.S.C. § 552(b), and reserve the right to appeal a decision to withhold any information or deny a waiver of fees.

Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street W6035
Baltimore, MD 21205
Phone: 410 955 8168
Fax: 410 955 0863
Email: galexan9@jhmi.edu

Please communicate any questions you may have by phone or email, rather than regular mail. Also, if the requested records cannot be provided by email, please notify me as soon as they are available and I will consider arranging to collect them by courier to avoid additional delay.

Your prompt attention to this request is greatly appreciated.

Respectfully,

G Caleb Alexander

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine